Age-Related Changes in 11β-Hydroxysteroid Dehydrogenase Type 2 Activity in Normotensive Subjects

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BACKGROUND
Impairment in 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) activity results in inefficient inactivation of cortisol to cortisone, and it can trigger hypertension through activation of the mineralocorticoid receptor. Information about age-related changes in 11β-HSD2 activity and its physiological consequences is scarce. Our aim was to investigate whether 11β-HSD2 activity is age dependent in normotensive subjects.

METHODS
We recruited 196 healthy, normotensive subjects. Of these, 93 were children (Group 1: aged 5–15 years), and 103 were adults who were divided according to their ages: Group 2: aged 30–41 years (n = 10); Group 3: aged 42–53 years (n = 72); and Group 4: aged 54–65 years (n = 21). Fasting serum cortisol, cortisone, aldosterone, and plasma renin activity (PRA) were measured. The 11β-HSD2 activity was estimated by the cortisol/cortisone ratio. The results were expressed as median (interquartile range (IQR)) values and compared using Kruskal–Wallis and Dunn’s multiple-comparison tests.

RESULTS
As subject age increased, cortisol concentrations increased (Group 1 median = 8.6, IQR = 6.3–10.8 µg/dl; Group 4 median = 12.4, IQR = 10.7–14.7 µg/dl; P < 0.001), and cortisone concentrations showed a gradual decrease (Group 2 median = 4.0, IQR = 3.3–4.2 µg/dl; Group 4 median = 2.8, IQR = 2.6–3.3 µg/dl; P < 0.01). As a consequence, the cortisol/cortisone ratio was higher in the oldest subjects (Group 4) than in the subjects from the other 3 groups; the ratios from Group 4 to Group 1 were 4.4 (IQR = 3.7–5.1) µg/dl, 3.3 (IQR = 2.7–3.8) µg/dl, 2.5 (IQR = 2.3–3.8) µg/dl, and 2.7 (IQR = 2.1–3.4) µg/dl, respectively (P < 0.01). The PRA decreased with age. Blood pressure levels increased with age but stayed within the normal range.

CONCLUSIONS
Cortisol and the cortisol/cortisone ratio increased with age, but cortisone decreased, suggesting a decrease in 11β-HSD2 activity. These results suggest that the cortisol-mediated activation of the mineralocorticoid receptor may explain the blood pressure increase in elderly subjects.

Keywords: age; blood pressure; essential hypertension; hypertension; 11β-HSD2 activity.

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The prevalence of arterial hypertension increases with age, although the cause in the majority of patients is unknown. There are several environmental and congenital factors that have been identified as risks factors for the development of hypertension, including family history of essential hypertension, age, race, obesity, and salt intake.1 Increased salt sensitivity is a characteristic of hypertension in elderly persons.2 Salt sensitivity in younger persons has been attributed, at least in part, to a reduced activity of the 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) enzyme activity.3,4 The impairment of 11β-HSD2 activity results in inefficient conversion of cortisol to its inactive metabolite cortisone, which may trigger hypertension through the activation of the mineralocorticoid receptor.5 The 11β-HSD2 enzyme is found predominantly in mineralocorticoid receptor (MR) target tissues such as the kidney, colon, salivary glands, and blood vessels,6 where it serves to protect the MR from excess glucocorticoids.

The classical view of hormone action in target organs is one in which hormones signal by the ligand binding to a specific cognate receptor. However, in mineralocorticoid target organs, hormonal specificity is determined by an enzyme rather than the receptor. The MR has equal affinity for cortisol and aldosterone in vitro,7 and the inactivation

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of cortisol to cortisone by 11β-HSD2 at the site of the MR enables aldosterone to bind its receptor in vivo.8 In addition, the concentration of cortisol in the systemic circulation is approximately 1,000-fold higher than that of aldosterone. Moreover, in animal models, there is an increase in the expression of the MR in the vascular wall with age.9

Congenital or acquired defects in this enzyme lead to cortisol-mediated mineralocorticoid excess. The former results from inactivating mutations in the HSD11B2 gene, resulting in a significant reduction of enzyme activity, and this is referred to as apparent mineralocorticoid excess (Online Mendelian Inheritance in Man No. 218030). Its clinical presentation includes low birth weight, failure to thrive, short stature, severe hypertension, hypokalemia, suppressed plasma renin activity (PRA), and undetectable aldosterone.10,11 Inhibition of the enzyme after ingestion of licorice or carbenoxolone or by adrenocorticotropic hormone (ACTH) excess (similar to that observed in ectopic ACTH syndrome) results in a similar, although milder, phenotype.12,13

Based on these findings, the 11β-HSD2 enzyme activity may be considered a key enzyme for maintaining the blood pressure (BP) within the normal range. To the best of our knowledge, no previous studies have addressed age-related changes in 11β-HSD2 activity in a healthy, normotensive population. The aim of this study was to investigate whether 11β-HSD2 activity is age dependent and if these changes are associated with a progressive mineralocorticoid receptor activation and an increase in BP in normotensive subjects along a wide age range.

METHODS

Study design and sample description

We designed a cross-sectional study and recruited 196 normotensive subjects (aged 5–65 years). Of these participants, 93 were children of normotensive parents (aged 5–15 years; 61% female), and 103 were normotensive adults who were divided into 3 groups according to their ages: aged 30–41 years (n = 10; 50% female); aged 42–53 years (n = 72; 77.9% female); and aged 54–65 years (n = 21; 71.4% female). None of the selected subjects were consuming licorice or receiving any antihypertensive therapy, and none of the women were using oral contraceptives or undergoing hormone replacement therapy.

Clinical characteristics and study protocol

All of the subjects underwent a complete physical exam. The children’s exams were performed by 2 pediatric endocrinologists (A.M.-A. and H.G.) and 1 pediatric nephrologist (M.A.). The subjects’ heights were measured using a wall-mounted Harpenden stadiometer Holtain (Crymych, Pembrokeshire, UK), and their weight and total fat mass percentage were assessed by bioelectrical impedance (Tanita, Corporation of America, Arlington Heights, IL). The children with severe obesity (z score > 2.5) were excluded. Pubertal development was assessed according to the Marshall and Tanner method.14

Trained nurses measured the BP and heart rate of all of the subjects. Three measurements were obtained from the right arm at consecutive 5-minute intervals using an oscillometric method (Dinamap CARESCAPE V100, GE Healthcare; Medical Systems Information Technologies, Inc., Milwaukee, WI, USA) with the patient in a seated position. This measurement was performed with a cuff and bladder that were size-adjusted to the subject’s upper-arm girth according to the published recommendations.15 Normotension in children was defined as an average systolic BP (SBP) and/or diastolic BP (DBP) lower than the 90th percentile for sex, age, and height. In adults, normotension was considered to be at least 2 different measurements of BP < 140/90 mm Hg.

Biochemical assays

Fasting blood samples (taken from 8:00–10:00 AM from a patient in the sitting position with at least a 15-minute rest) were obtained to measure levels of sodium, potassium, creatinine, cortisol, cortisone, plasma renin activity, and aldosterone. Previously described methods were used for these measurements.16 The 11β-HSD2 activity was estimated based on the serum cortisol/cortisone ratio, which our experience has shown to be a useful tool.1,3,4 At the same time, 12-hour nocturnal urine (between 7:00 PM and 7:00 AM, next day) samples were collected from the children, and 24-hour urine samples were collected from the adults. Total 12-hour and 24-hour urine volumes were measured, and 50-ml aliquots were stored to measure the creatinine and sodium contained therein. Sodium excretion was corrected for by urinary creatinine. The serum, plasma, and urine samples were stored in aliquots at −80 °C until they were analyzed.

Ethics

The protocol followed in this study was written according to the guidelines of the Declaration of Helsinki and approved by the Ethical Committee of the Faculty of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile. The study and protocol were explained to all participants. All of the parents signed informed consent forms, and subjects who were aged >7 years also provided their consent before enrolling in the study.

Data analysis

The results were expressed as median values (interquartile range (IQR)). The comparisons between the children and the 3 adult groups were performed by the Kruskal–Wallis and Dunn’s multiple comparison tests. For children, the body mass index (BMI) was calculated and converted to a standard deviation score (SDS) using Epinut software (public domain statistical software for epidemiology developed by Centers for Disease Control and Prevention (CDC) in Atlanta, GA). To analyze the changes in the nutritional status of the 4 age groups, we divided the subjects in groups of normal and overweight–obese malnutrition. Male and female children were considered to be overweight or obese if their BMI was greater than the 85th percentile (or BMI SDS ≥ 1.04); adults were considered overweight or obese when their BMI was ≥ 25 kg/m², according to the definition of the World Health Organization (http://www.who.int/mediacentre/factsheets/
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The distribution of nutritional status between children and adults was compared by the χ² test. The Pearson correlation was used to analyze the association between 2 variables. The values of serum cortisol, the cortisol/cortisone ratio, plasma renin activity, and aldosterone were logarithmically transformed to achieve a normal distribution before they were subjected to Pearson association analysis. Stepwise multiple regression analyses were used to quantify the independent contributions of the log₁₀ age and BMI to the variance of log₁₀ cortisol/cortisone ratio and log₁₀ PRA, respectively, and to examine the independent contributions of log₁₀ age and BMI to the variance of SBP and DBP, respectively. Differences were considered statistically significant at P < 0.05. Statistical analysis was performed using the SPSS 15.0 program for Windows (SPSS, Chicago, IL).

RESULTS

Clinical and biochemical characteristics

The clinical and biochemical characteristics of normotensive subjects (children and adults) are shown in Table 1. Because the nutritional status classifications require the BMI (SDS) of the children, we compared the distributions of nutritional status between the groups after categorizing the subjects as eutrophic or overweight and obese. Obesity was observed in 44 of 93 (47.3%) subjects in the group aged 5–15 years, in 9 of 10 (90%) subjects in the group aged 30–41 years, in 57 of 72 (79.2%) subjects in the group aged 42–53 years, and in 21 of 21 (100%) subjects in the group aged 54–65 years, indicating that a higher proportion of the adults (n = 103) than of the children were obese (P < 0.0001, χ² test). In the adult groups, the median BMI value was higher in the group aged 54–65 years than in the group aged 42–53 years (P < 0.05).

In the entire group, SBP showed a positive association with the log₁₀ of age (Pearson r = 0.731; P < 0.0001) and with BMI (Pearson r = 0.665; P < 0.0001); DBP also showed a positive association with the log₁₀ of age (Pearson r = 0.651; P < 0.0001) and with BMI (Pearson r = 0.618; P < 0.0001). SBPs and DBPs were lower in children than in the 3 adult groups, although SBP and DBP were within the normal range (Table 1).

Next, we performed multiple regression analysis to examine the independent contributions of log₁₀ age and BMI to the variance of SBP and DBP in the entire group. In this statistical model, the log₁₀ age variable contributed most strongly

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### Table 1. Clinical and biochemical characteristics of the normotensive subjects studied

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5–15</td>
</tr>
<tr>
<td>No.</td>
<td>93</td>
</tr>
<tr>
<td>Sex, women/men</td>
<td>52/41</td>
</tr>
<tr>
<td>Age, years</td>
<td>10.7 (8.7–12.6)a,b,c</td>
</tr>
<tr>
<td>BMI, SDS kg/m²</td>
<td>0.96 (0.17–1.50)</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>102 (97–110)</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>63 (59–67)</td>
</tr>
<tr>
<td>Serum Sodium, mEq/l</td>
<td>141 (140–142)</td>
</tr>
<tr>
<td>Potassium, mEq/l</td>
<td>4.3 (4.1–4.6)d</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.52 (0.47–0.62)b,c</td>
</tr>
<tr>
<td>Cortisol, µg/dl</td>
<td>8.6 (6.3–10.8)d</td>
</tr>
<tr>
<td>Cortisone, µg/dl</td>
<td>3.2 (2.8–3.7)</td>
</tr>
<tr>
<td>Cortisol/cortisone ratio</td>
<td>2.7 (2.1–3.4)b,c</td>
</tr>
<tr>
<td>Aldosterone, ng/dl</td>
<td>6.8 (3.2–9.7)</td>
</tr>
<tr>
<td>PRA, ng/ml × h</td>
<td>2.5 (1.7–3.6)b,c</td>
</tr>
<tr>
<td>ARR</td>
<td>2.6 (1.6–4.1)b,c</td>
</tr>
<tr>
<td>Urine Sodium, mEq/g creatinine</td>
<td>152 (121–223)</td>
</tr>
</tbody>
</table>

Values correspond to medians (interquartile range).

Abbreviations: ARR, aldosterone/plasma renin activity ratio; BMI, body mass index; DBP, diastolic blood pressure; PRA, plasma renin activity; SBP, systolic blood pressure; SDS, standard deviation score.

a P < 0.05 vs. group of subjects aged 30–40 years.
b P < 0.05 vs. group of subjects aged 42–53 years.
c P < 0.05 vs. group of subjects aged 54–65 years.
d P < 0.05 for group of subjects aged 30–41 years vs. group of subjects aged 42–53 years.
e P < 0.05 for group of subjects aged 30–41 years group vs. group of subjects aged 54–65 years.
f P < 0.05 for group of subjects aged 42–53 years group vs. group of subjects aged 54–65 years.
to the changes in SBP ($\beta = 0.730; \ R^2 = 0.531; P < 0.0001$), and variance ($R^2$) increased only marginally (2%) when BMI was added to the model ($\beta = 0.238; \ R^2 = 0.551; P = 0.002$). The log$_{10}$ age variable largely accounted for changes in DBP ($\beta = 0.656; \ R^2 = 0.427; P < 0.0001$), and variance ($R^2$) again increased only marginally (3.6%) when BMI was added to the model ($\beta = 0.314; \ R^2 = 0.463; P < 0.0001$).

In the pediatric group, SBP showed a positive association with the log$_{10}$ of age (Pearson $r = 0.535; P < 0.0001$) and BMI (SDS) (Pearson $r = 0.298; P = 0.004$); DBP showed a positive association with the log$_{10}$ of age (Pearson $r = 0.276; P = 0.007$) and BMI (SDS) (Pearson $r = 0.313; P = 0.002$). Next, we performed a multiple regression analysis to examine the independent contributions of log$_{10}$ age and BMI (SDS) to the variance of SBP. In this statistical model, the log$_{10}$ age variable explains the changes in SBP ($\beta = 0.535; \ R^2 = 0.278; P < 0.0001$), and variance ($R^2$) increased (6.8%) when BMI (SDS) was added to the model ($\beta = 0.273; \ R^2 = 0.346; P = 0.002$). We also performed a multiple regression analysis to examine the independent contributions of log$_{10}$ age and BMI (SDS) to the variance of DBP. In this statistical model, the BMI (SDS) explains the changes in DBP ($\beta = 0.313; \ R^2 = 0.088; P < 0.002$), and variance ($R^2$) increased (6.0%) when log$_{10}$ age was added to the model ($\beta = 0.261; \ R^2 = 0.148; P = 0.008$). In the adult group, the log$_{10}$ age was not associated with SBP (Pearson $r = 0.165; P = 0.095$) or DBP (Pearson $r = 0.060; P = 0.55$). No association was observed between BMI and SBP (Pearson $r = -0.155; P = 0.12$), although BMI did show a positive association with DBP (Pearson $r = 0.207; P = 0.04$). All subjects showed normal renal function as measured by their serum creatinine concentrations. As expected, the children showed lower serum creatinine concentrations than the adults. Pediatric and adult groups showed similar urinary sodium excretion (Table 1).

**Age-related changes in serum cortisol and cortisone concentrations**

The concentrations of matinal serum cortisol were observed to increase throughout life, although they remained within the normal range (log$_{10}$ serum cortisol vs. log$_{10}$ age: Pearson $r = 0.193; P = 0.007$). The levels were higher in subjects aged 54–65 years than in children aged 5–15 years and adults aged 42–53 years (Figure 1a; Table 1). This increase in serum cortisol concentration was independent of the nutritional status of the subjects. Serum cortisol concentration did not show an association with BMI (SDS) in children (n = 93; Pearson $r = 0.079; P = 0.499$) or with BMI in adults (n = 103; Pearson $r = 0.064; P = 0.52$).

In contrast, matinal serum cortisone concentration tended to be higher in the children and the younger adults, but then serum cortisone concentrations declined with age. The concentration was higher in the youngest adult subjects (aged 30–41 years) than in the subjects aged 42–53 years or 54–65 years (Figure 1b; Table 1).

**Age-related changes in the cortisol/cortisone ratio**

The observed serum cortisol/cortisone ratios increased with advancing age. The oldest normotensive group (aged 54–65 years) showed higher cortisol/cortisone ratios than the younger normotensive groups (Figure 1c; Table 1). This ratio showed similar values only between the groups of normotensive subjects aged 5–15 years and 30–41 years. As a consequence of the increased cortisol levels and the decreased cortisone concentrations observed in the group of subjects aged 55–65 years, the cortisol/cortisone ratio was higher than that observed in the younger subjects (Figure 1c). As expected, we found a positive association between log$_{10}$ age and log$_{10}$ serum cortisol/cortisone ratio in the adult groups but not in children (Pearson $r = 0.348; P < 0.0001$; Pearson $r = -0.104; P = 0.32$, respectively). The observed association between age and serum cortisol/cortisone ratio was independent of BMI. In both children and adults, no association was observed between the log$_{10}$ serum cortisol/cortisone ratio and BMI (Pearson $r = -0.006, P = 0.96$; Pearson $r = 0.118, P = 0.24$, respectively). The cortisol/cortisone ratio was also associated with BP in the entire group (Figure 2), and the log$_{10}$ serum cortisol/cortisone ratio showed a positive correlation with SBP ($n = 196; Pearson r = 0.2175; P = 0.002$) and with DBP ($n = 196; Pearson r = 0.1916; P = 0.007$).

**Angiotensin-aldosterone system and 11β-HSD2 activity**

PRA was also observed to decline with age. The PRA values of the normotensive children were higher than those observed in the normotensive adults (aged 42–53 years and 54–65 years), as shown in Figure 1d and Table 1 (log$_{10}$ PRA vs. log$_{10}$ age: $n = 196; Pearson r = -0.591; P < 0.0001$). The aldosterone concentration tended to decrease with age, although this trend did not reach statistical significance (log$_{10}$ aldosterone vs. log$_{10}$ age; Pearson $r = -0.129; P = 0.07$). Moreover, the log$_{10}$ PRA was negatively associated with the log$_{10}$ cortisol/cortisone ratio (Pearson $r = -0.148; P = 0.04$, for the entire group). Next, we performed multiple regression analysis to examine the independent contributions of log$_{10}$ age and log$_{10}$ cortisol/cortisone ratio to the variance of log$_{10}$ PRA. In this statistical model, log$_{10}$ age was the only variable that explained changes in the log$_{10}$ PRA ($\beta = -0.591; R^2 = 0.346; P < 0.0001$).

**DISCUSSION**

The results of this study show an inverse age-related concentration in serum cortisol and cortisone concentrations in healthy, normotensive subjects. The serum cortisone concentration decreases significantly after the fourth decade of life, whereas the cortisol concentration increases. Consequently, the serum cortisol/cortisone ratio increases and BP rises. This process may contribute to the development of hypertension in elderly subjects because cortisol binds as avidly to the mineralocorticoid receptor as aldosterone.18

As far as we know, there is scant information about the changes in 11β-HSD2 enzyme activity throughout the life of healthy subjects. Dötsch et al.19 analyzed the changes in serum cortisol, cortisone, and the cortisol/cortisone ratio in healthy children and adolescents (aged < 1 month to 18 years). Their results showed that the serum cortisol/cortisone ratio rose significantly during the first year of life but did not change afterward. Unfortunately, this study did not
include healthy adult subjects. Consistent with this previous data, we did not observe changes in the serum cortisol/cortisone ratio within the subjects aged 5–15 years. More recently, Henschkowski et al. reported that 11β-HSD2 activity declines with age in hypertensive patients from 18 to 84 years. Their results are addressed in the same direction as ours, but they did not study normotensive subjects. Unlike us, they estimated the enzyme activity by measuring the urinary cortisol/cortisone ratio, and they did not investigate if there was an association between cortisol/cortisone ratio and mineralocorticoid status.

Interestingly, our results show that the gradual shift of endogenous glucocorticoids to more mineralocorticoid activity after the fourth decade of life is reflected in the decreased plasma renin activity that was observed during the same period of time. Thus, we can speculate that the appearance of hypertension is initiated by a decrease in 11β-HSD2 activity, which leads to reduced cortisol inactivation and allows activation of the mineralocorticoid receptor. This could trigger hyporeninemic hypertension in the future.

Although the PRA declined with age, the values seem sufficient to maintain aldosterone levels within the normal range. Notably, the blood samples from all subjects were drawn between 8:00 AM and 10:00 AM (when cortisol concentrations were higher) to facilitate the detection of slight defects in 11β-HSD2 enzyme activity. The higher concentration of cortisol provides more substrate for the enzyme to inactivate.

Figure 1. Age-related changes in serum cortisol, cortisone, cortisol/cortisone ratio and plasma renin activity in normotensive subjects. (a) Age-related changes in serum cortisol concentration. (b) Age-related changes in serum cortisone concentration. (c) Age-related changes in serum cortisol/cortisone ratio. (d) Age-related changes in plasma renin activity in normotensive subjects. Group aged 5–15 years: n = 93; group aged 30–41 years: n = 10; group aged 42–53 years: n = 72; and group aged 54–65 years: n = 21.
were higher in the morning than in the evening in healthy adult volunteers (aged 21–46 years), suggesting that the activity of this enzyme does not show a circadian variation.

The decrease in 11β-HSD2 enzyme activity may be related to several nutritional and environmental changes that occur during the lifetime. Caffeine and its primary metabolite paraxanthine have been demonstrated to inhibit expression and activity of 11β-HSD2. A similar observation was described for licorice, a sweetener containing glycyrrhetinic acid, and recently a high salt intake was also implicated in declining \( HSD11B2 \) gene expression. In addition, the reported environmental disruptors gossypol, phthalates, organotins, alkylphenols, and textiles, paper, and upholstery, and as reaction additives in various processes. An increase in the concentration of endogenous inhibitors may also decrease enzyme activity. Another factor that could stimulate the expression of 11β-HSD2 mRNA is growth hormone, and because it decays with age, the decrease in the enzymatic activity may also be explained. Paulsen et al. reported that growth hormone treatment was able to increase levels of 11β-HSD2 messenger RNA and decrease those of 11β-HSD1 messenger RNA in adipose tissue, and accordingly, it may be able to reduce the amount of locally produced cortisol.

Another important point is that the expression of the 11β-HSD2 enzyme may diminish with age because of epigenetic changes such as DNA methylation. The \( HSD11B2 \) gene is susceptible to methylation because it has major CpG islands in the promoter, exon 1, and exon 5. Methylation is a mechanism known to affect \( HSD11B2 \) gene expression. Additionally, demethylation enhances \( HSD11B2 \) gene transcription and 11β-HSD2 enzyme activity in vivo in rats and in vitro, and Friso et al. recently noted that elevated \( HSD11B2 \) promoter methylation was associated with hypertension development in glucocorticoid-treated patients.

One of the strengths of this study is that we analyzed healthy normotensive volunteers with a wide age range (aged 5–65 years). However, this can also be a limitation because this is a cross-sectional study and not a longitudinal study for analyzing the changes along 6 decades of the life in the same subjects. Another limitation is that there are several known and unknown changes that could affect the 11β-HSD2 enzyme activity, such as coffee intake of the participants, which was not consigned at the time of this study.

In summary, our results show a gradual and progressive age-related decline in the 11β-HSD2 enzyme activity of normotensive subjects, an effect that could cause cortisol-mediated mineralocorticoid receptor activation and that could explain, at least in part, the appearance of hypertension in elderly subjects.

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**Disclosure**

The authors declared no conflict of interest.